

**BIOGRAPHICAL SKETCH**

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NAME: Brenner, Andrew

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Associate Professor of Medicine, Neurology, and Neuro-Surgery

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Texas A&M University , College Station, Tx	BS	05/1993	Biochemistry
University of Texas at Austin (MD Anderson CC Science Park), Austin, Tx	PHD	05/1997	Tumor Biology
Texas Tech Univ Health Science Center, Lubbock, Tx	MD	05/2003	Medicine
European Institute of Oncology, Milan	Postdoctoral Fellow	08/1999	Cell Cycle and Breast Cancer
Texas A&M University HSC Scott and White Hospital, Temple, Tx	Resident	06/2006	Internal Medicine
University of Texas Health Science Center at San Antonio, San Antonio, Tx	Other training	06/2008	Medical Oncology

**A. Personal Statement**

I am a medical oncologist and tumor biologist with an interest in drug development for the management of primary brain tumors and breast neoplasms. At the basic research level, my interests are in developing novel therapeutics for the treatment of malignancy with a focus on overcoming resistance to conventional therapeutics. To this end we have developed a number of animal models which allow assessment of the impact of different therapies on animal survival, and in particular the means of tumor adaptation. Many of these studies have resulted in clinical trials in patients which currently span from first in human (phase 1) through pivotal phase 3. This experience includes navigation of regulatory processes including IND enabling studies, authoring study protocols, coordinating multicenter studies, as well as acting as principal investigator of 14 industry and investigator initiated phase 1 trials since 2008.

1. Sareddy GR, Li X, Liu J, Viswanadhapalli S, Garcia L, Gruslova A, Cavazos D, Garcia M, Strom AM, Gustafsson JA, Tekmal RR, Brenner A, Vadlamudi RK. Selective Estrogen Receptor  $\beta$  Agonist LY500307 as a Novel Therapeutic Agent for Glioblastoma. Sci Rep. 2016 Apr 29;6:24185. PubMed PMID: [27126081](#); PubMed Central PMCID: [PMC4850367](#).
2. Gruslova A, Cavazos DA, Miller JR, Breitbart E, Cohen YC, Bangio L, Yakov N, Soundararajan A, Floyd JR, Brenner AJ. VB-111: a novel anti-vascular therapeutic for glioblastoma multiforme. J Neurooncol. 2015 Sep;124(3):365-72. PubMed PMID: [26108658](#); PubMed Central PMCID: [PMC4584173](#).
3. Brenner AJ, Cohen YC, Breitbart E, Bangio L, Sarantopoulos J, Giles FJ, Borden EC, Harats D, Triozzi PL. Phase I dose-escalation study of VB-111, an antiangiogenic virotherapy, in patients with advanced solid tumors. Clin Cancer Res. 2013 Jul 15;19(14):3996-4007. PubMed PMID: [23589178](#).
4. Drappatz J, Brenner A, Wong ET, Eichler A, Schiff D, Groves MD, Mikkelsen T, Rosenfeld S, Sarantopoulos J, Meyers CA, Fielding RM, Elian K, Wang X, Lawrence B, Shing M, Kelsey S, Castaigne JP, Wen PY. Phase I study of GRN1005 in recurrent malignant glioma. Clin Cancer Res. 2013 Mar 15;19(6):1567-76. PubMed PMID: [23349317](#).

## **B. Positions and Honors**

### **Positions and Employment**

- 2008 - 2015     Assistant Professor of Medicine, University of Texas Health Science Center at San Antonio, Cancer Therapy and Research Center, Division of Hematology and Medical Oncology, San Antonio, TX
- 2011 -           S&B Kolitz / Zachary Endowed Chair in Neuro-Oncology Research, University of Texas Health Science Center at San Antonio
- 2013 -           Adjunct Assistant Professor, University of Texas at Austin, Austin, TX
- 2015 -           Co-Leader, Experimental Therapeutics Program, Cancer Therapy and Research Center at UTHSCSA, Cancer Center Support Grant (P30)
- 2015 -           Medical Director, Cancer Therapy and Research Center at UTHSCSA
- 2015 -           Associate Professor of Medicine, Neurology, and Neuro-Surgery, University of Texas Health Science Center at San Antonio, San Antonio, TX

### **Other Experience and Professional Memberships**

- 2000 - 2001     Committee on Cancer, Texas Medical Association
- 2005 - 2007     Council on Scientific Affairs, Special Appointee, Texas Medical Association
- 2006 -           Board Certification, American Board of Internal Medicine, Internal Medicine
- 2008 -           Board Certification, American Board of Internal Medicine, Medical Oncology
- 2008 -           Institutional Review Board Member, University of Texas Health Science Center at San Antonio
- 2008 - 2013     Data Safety Monitoring Committee, Cancer Therapy and Research Center at UTHSCSA
- 2012 -           Oncology Unit Medical Director, St. Lukes Baptist Hospital
- 2013 -           Certification, Neuro-Oncology, United Council of Neurologic Subspecialties
- 2013 -           Institutional Biosafety Committee Member, University of Texas Health Science Center at San Antonio

### **Honors**

- 1992             Outstanding Undergraduate Biochemist for 1992, Texas A&M University
- 1992             Nestor R. Bottino Award for Aptitude and Excellence in Research, Texas A&M University
- 1993             HEB Foundation Predoctoral Fellowship, UT MD Anderson Cancer Center, Science Park, Research Division
- 2000             Carmela Gigliardi Scholarship, National Italian American Foundation
- 2012             2012 Clinical Investigator Award, Cancer Therapy and Research Center at UTHSCSA

## **C. Contribution to Science**

1. In order to better understand the underlying mechanisms responsible for worsened outcomes of obese breast cancer patient, we began analyzing serum from our patients and applying an in vitro model of estrogen receptor positive breast cancer. These experiments showed that serum from obese breast cancer patients reflected a systemic inflammatory state which resulted in activation of the aromatase gene. The net effect was increased local production of estrogen within the breast of obese women. Analysis of retrospective clinical data suggested that this could be pharmacologically acted upon by COX2 inhibition. A pilot randomized study of 120 subjects has been completed (Brenner PI), and a randomized cooperative group study is planned (Brenner Study Chair).
  - a. Bowers LW, Cavazos DA, Maximo IX, Brenner AJ, Hursting SD, deGraffenried LA. Obesity enhances nongenomic estrogen receptor crosstalk with the PI3K/Akt and MAPK pathways to promote in vitro measures of breast cancer progression. Breast Cancer Res. 2013;15(4):R59. PubMed PMID: [23880059](#); PubMed Central PMCID: [PMC3978844](#).
  - b. De Angel RE, Conti CJ, Wheatley KE, Brenner AJ, Otto G, Degraffenried LA, Hursting SD. The

enhancing effects of obesity on mammary tumor growth and Akt/mTOR pathway activation persist after weight loss and are reversed by RAD001. *Mol Carcinog*. 2013 Jun;52(6):446-58. PubMed PMID: [22290600](#).

- c. Bowers LW, Maximo IX, Brenner AJ, Beeram M, Hursting SD, Price RS, Tekmal RR, Jolly CA, deGraffenried LA. NSAID use reduces breast cancer recurrence in overweight and obese women: role of prostaglandin-aromatase interactions. *Cancer Res*. 2014 Aug 15;74(16):4446-57. PubMed PMID: [25125682](#).
  - d. Bowers LW, Brenner AJ, Hursting SD, Tekmal RR, deGraffenried LA. Obesity-associated systemic interleukin-6 promotes pre-adipocyte aromatase expression via increased breast cancer cell prostaglandin E2 production. *Breast Cancer Res Treat*. 2015 Jan;149(1):49-57. PubMed PMID: [25476497](#); PubMed Central PMCID: [PMC4409140](#).
2. My early publications were instrumental in helping to define the role of the CDK4/6 inhibitor p16 CDKN2A (INK4A) in breast tumorigenesis and immortalization of breast epithelium. These publications found that while CDKN2A is not a target of mutation, it is frequently affected by a combination of deletion and epigenetic modification resulting in loss of expression in the majority of breast cancers. Additionally, the loss of p16 expression in normal human mammary epithelial cells by promoter methylation conferred an extended replicative capacity. Cumulatively, these findings support p16 CDKN2A as a gene of relevance to breast tumorigenesis and escape from senescence.
- a. Brenner AJ, Stampfer MR, Aldaz CM. Increased p16 expression with first senescence arrest in human mammary epithelial cells and extended growth capacity with p16 inactivation. *Oncogene*. 1998 Jul 16;17(2):199-205. PubMed PMID: [9674704](#).
  - b. Bednarek AK, Sahin A, Brenner AJ, Johnston DA, Aldaz CM. Analysis of telomerase activity levels in breast cancer: positive detection at the in situ breast carcinoma stage. *Clin Cancer Res*. 1997 Jan;3(1):11-6. PubMed PMID: [9815531](#).
  - c. Brenner AJ, Paladugu A, Wang H, Olopade OI, Dreyling MH, Aldaz CM. Preferential loss of expression of p16(INK4a) rather than p19(ARF) in breast cancer. *Clin Cancer Res*. 1996 Dec;2(12):1993-8. PubMed PMID: [9816158](#).
  - d. Brenner AJ, Aldaz CM. Chromosome 9p allelic loss and p16/CDKN2 in breast cancer and evidence of p16 inactivation in immortal breast epithelial cells. *Cancer Res*. 1995 Jul 1;55(13):2892-5. PubMed PMID: [7796417](#).
3. While not a significant focus of my research, my early post-graduate training work also included characterization of a powered bone marrow biopsy system. Our studies were not only the first in humans of this now commonly used powered biopsy device, but they also established the superiority of a powered biopsy system in both specimen quantity and level of patient discomfort.
- a. Swords RT, Kelly KR, Cohen SC, Miller LJ, Philbeck TE, Hacker SO, Spadaccini CJ, Giles FJ, Brenner AJ. Rotary powered device for bone marrow aspiration and biopsy yields excellent specimens quickly and efficiently. *J Clin Pathol*. 2010 Jun;63(6):562-5. PubMed PMID: [20404008](#).
  - b. Miller LJ, Philbeck TE, Montez DF, Puga TA, Brodie KE, Cohen SC, Spadaccini C, Swords R, Brenner AJ. Powered bone marrow biopsy procedures produce larger core specimens, with less pain, in less time than with standard manual devices. *Hematol Rep*. 2011 Jan 13;3(1):e8. PubMed PMID: [22184530](#); PubMed Central PMCID: [PMC3238476](#).
  - c. Swords RT, Anguita J, Higgins RA, Yunes AC, Naski M, Padmanabhan S, Kelly KR, Mahalingam D, Philbeck T, Miller L, Puga TA, Giles FJ, Kinney MC, Brenner AJ. A prospective randomised study of a rotary powered device (OnControl) for bone marrow aspiration and biopsy. *J Clin Pathol*. 2011 Sep;64(9):809-13. PubMed PMID: [21606230](#).

## **D. Additional Information: Research Support and/or Scholastic Performance**

### **Ongoing Research Support**

01 CA178499-01A1, National Cancer Institute (NCI) Brenner, Andrew (PI) 09/01/14-08/31/19  
Novel ERbeta agonists for the treatment of gliomas  
Role: CPI

DP150021, Cancer Prevention Research Institute of Texas Brenner, Andrew (PI) 05/01/15-01/01/18  
NanoTx Therapeutics New Company Product Development Award  
Funds are made available to support the establishment of a new company with the goal of development and commercialization of liposomally encapsulated therapeutic radionuclides for the treatment of cancer,  
Role: PI

RP130548, Cancer Prevention and Research Institute of Texas Brenner, Andrew (PI) 06/01/13-11/30/16  
Overcoming CXCL12 Mediated Resistance in Glioblastoma  
The specific aims are: 1. Establish the CXCR4 and CXCR7 dependent effects of CXCL12 on vascularization and tumor cell migration. 2. Evaluate the relative contribution of CXCR4 and CXCR7 to glioma survival, endothelial survival, and expansion of the glioma stem-like cell niche with exposure to antiangiogenics or hypoxia. 3. Characterize the mechanisms by which CXCR7 signaling promotes stem like tumor cell survival.  
Role: PI

R01 FD004400-02 Brenner, Andrew Jacob (PI) 08/01/14-06/30/18  
Phase 2 Study of TH-302 for the Treatment of Glioblastoma  
Role: PI

P30CA054174, National Institutes of Health / National Cancer Institute Brenner, Andrew (PI) 08/01/14-07/31/19  
Cancer Therapy & Research Center at UTHSCSA  
This cancer center support grant provides research core and program infrastructure support to members of the cancer center for the conduct of their cancer-related research.  
Role: Co-Investigator

### **Completed Research Support**

R01 FD004400-01A2 Brenner, Andrew Jacob (PI) 08/01/14-06/30/15  
Phase 2 Study of TH-302 for the Treatment of Glioblastoma  
Role: PI

L30 CA154152-03 Brenner, Andrew Jacob (PI) 07/01/14-06/30/15  
Novel Treatment for Glioblastoma  
Role: PI

A major paradigm shift in the management of breast cancer over the past decade has been implementation of a personalized approach toward treatment decisions(1). TCGA (2) data has shown us that breast cancer can be primarily clustered into at least four subtypes and that each subtype has a number of potentially targetable alterations which could be exploited to change patient outcomes. However, it also showed marked heterogeneity at the genetic level within a subgroup and suggested a clonal plasticity that may highlight adaptive resistance to this approach. An alternate approach to personalizing therapy based upon a comprehensive profile is to perform Gene Set Enrichment Analysis (GSEA) using canonical pathway gene sets. By doing so, one can focus on understanding high-level functions and utilities of the cancer cell rather than changes in individual genes. In applying The Broad Institutes GSEA tool and the Canonical Pathways genes sets database to the TCGA breast carcinoma mRNA-Seq dataset, seven subtype clusters are identified(3). In clusters 3 and 4, the top enriched pathway by level of significance was fatty acid metabolism, followed in cluster 3 by steroid hormone biosynthesis.

Given the changes of fatty acid metabolism in breast cancer, a dose expansion cohort at the recommended phase 2 dose in metastatic breast cancer patients was performed. Fifteen patient were enrolled, and represented a heavily pretreated population with an average 7 prior regimens and all considered taxane resistant. The results were considered impressive for this patient population, with 3 complete responders (20%), and an additional 11 of 15 patients obtaining stable disease beyond 10 weeks for a clinical benefit rate of 93%. Interestingly, while high FASN expression was relatively sensitive for predicting response, it was by no means specific as a significant percentage of patients with low FASN expression had significant stabilization of disease and included our longest responders (Figure 3B). This highlights the complexity of developing a biomarker for a metabolic inhibitor as a single target gene is inadequate for understanding the overall metabolic dependency within an individual's tumor. It is also our contention that in order to maximize the potential of this therapy a means of prospectively identifying patients sensitive to FASN inhibition is needed.

## **B. HYPOTHESIS AND SPECIFIC AIMS**

It is our specific hypothesis that tumor dependence on fatty acid synthesis can be determined using a liquid biopsy approach, and that this can be performed in a clinically meaningful timeframe. Further, this can then be validated in a prospective clinical trial of TVB-2640 in metastatic breast cancer. We therefore propose the following specific aims:

1. **Characterization of KEGG fatty acid metabolism gene set expression from circulating tumor cells (CTCs).**  
Patients with metastatic breast cancer of each TCGA subtype (4 per major subtype) will undergo phlebotomy contemporaneous to any planned biopsy procedure. CTCs will be isolated, and each CTC cell subject to 48 gene profiling using a BioMark Fluidigm QT-PCR system. Expression profiles will be compared with contemporaneous biopsy specimens.
2. **Metabolomic profiling and microvessel analysis.** Concentration and size distribution will be measured by Nanoparticle Tracking Analysis. Endogenous and exogenous metabolite profiling will be performed using magnetic resonance spectroscopy. Microvessel mRNA expression will be analyzed using the Biomark Fluidigm TaqMan Human mRNA Array by qRT-PCR.

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